In This Issue

Cell

Pathogens, Hosts, and Immunity

Photo courtesy of World Health Organization/Marko Kokic.

Recent news reports about avian influenza and the rise of multidrug resistant bacteria have heightened awareness about pathogen evolution and disease transmission in humans. Infectious diseases like tuberculosis, malaria, and AIDS affect millions of people and have a significant impact on the global economy. Plant pathogens have a tremendous impact on both agriculture and the natural environment.

In this special issue of *Cell*, our Leading Edge Commentaries, Essays, and Analysis focus on global health issues that set the context for basic research on host-pathogen interactions. The Review articles in this issue examine the factors that make some microbes more pathogenic than others and explore the constantly evolving relationship between pathogens and immune systems in both animals and plants. They offer insights that may one day prove useful in combating infectious diseases.

We are pleased to present a series of articles from distinguished experts in the field, and we thank all the authors who have committed their time and thoughts to make this issue possible. We hope that you find the articles exciting and informative.

Emerging and Re-Emerging Diseases

Infectious diseases are a leading cause of human morbidity and mortality, particularly in developing countries. Two Commentaries discuss the factors underlying the emergence of infectious diseases. **Anthony S. Fauci** (PAGE 665) uses influenza as an example of a seasonal human disease with the potential to erupt into a human pandemic. He discusses the factors that make some influenza viruses, such as the H1N1 pathogen that caused the Spanish Flu of 1918, extremely virulent. **David L. Heymann** (PAGE 671) addresses the issue of drug resistance in bacteria, viruses, and parasites and details some relatively simple measures that can be undertaken to reduce the emergence and prevalence of multi-drug-resistant pathogens.

Pathogenic Virulence Mechanisms

Several Review articles in this issue focus on our current understanding of pathogen biology. **David M. Raskin, Rekah Seshadri, Stefan U. Pukatzki, and John J. Mekalanos** (PAGE 703) highlight recent advances in genomic technology that provide new insights into the mechanisms of bacterial pathogenesis. They discuss how comparative genomic analyses can be used to identify virulence factors and to understand the ability of pathogens to adapt to particular host environments.

Four Reviews examine the mechanisms used by pathogenic microbes to invade and move within their target host cells. **Javier Pizarro-Cerdá and Pascale Cossart** (PAGE 715) describe adhesion molecules and macromolecular machines that allow bacteria to attach to and invade host cells and tissues. They identify several themes in bacterial invasion including the use of the bacterial Type III Secretion System, the requirement for membrane microdomains in the host, and the use of the host's endocytic and signaling pathways. **Mark Marsh and Ari Helenius** (PAGE 729) provide the viral perspective on invasion. They describe how viruses use the physiology of the host to their advantage, relying on host signaling pathways to induce cellular changes that aid viral entry and replication. Once within host cells, viruses use the host's cytoskeleton to move around and to transmit viral particles from cell to cell, a topic covered by **Urs F. Greber and Michael Way** (PAGE 741). Finally, **Alan F. Cowman and Brendan S. Crabb** (PAGE 755) review the mechanisms used by the malaria parasite to gain entry into host red blood cells. Unlike bacteria and viruses, these parasites do not depend on host factors for entry, but rather use their own machinery and an actin-myosin motor to invade target cells.

Host Immune Mechanisms

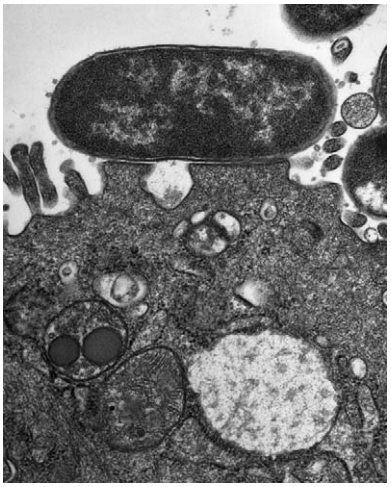
Both plants and animals have evolved sophisticated defense systems to protect themselves against pathogens. One common theme is the recognition of pathogen-associated molecular patterns, or PAMPs. **Shizuo Akira, Satoshi Uematsu, and Osamu Takeuchi** (PAGE 783). survey mammalian PAMP receptors, focusing on Toll-like receptors and their unique specificities for viral, bacterial, fungal, and parasitic antigens. They also review the roles of macrophages and dendritic cells in innate immunity. The Review by **Stephen T. Chisholm, Gitta Coaker, Brad Day, and Brian J. Staskawicz** (PAGE 803) examines pathogen resistance pathways in plants. The authors cover both PAMP-triggered immunity and the surveillance system, in which "R" proteins detect and respond to cellular changes brought on by pathogenic virulence proteins. The Review highlights the continuing interplay between pathogenic effectors and resistance pathways and examines how each has influenced the development and evolution of the other. **Max D. Cooper and Matthew N. Alder** (PAGE 815) also adopt an evolutionary perspective in their discussion of the adaptive branch of the vertebrate immune system. They describe how the jawed and jawless vertebrate lineages have both evolved an adaptive immune system based on recombinatorial rearrangement of cell surface receptors. However, each lineage uses a different type of receptor to generate diversity, suggesting convergent evolution. The authors speculate on the pressure to evolve such a system and the benefits of adaptive immunity.

Successful pathogens have evolved their own sophisticated mechanisms to evade detection and destruction by the host's immune system. A survey of pathogenic viruses and bacteria reveals some common evasive themes, as discussed by **Brett B. Finlay and Grant McFadden** (PAGE 767). These strategies include the manipulation and inhibition of the host's immune pathways, masking of antigenic surface proteins with carbohydrates, and antigenic variation.

Examining Factors that Influence the Outcome of an Infection

The outcome of an encounter between a pathogen and its host is determined not only by factors specific to the pathogen, but also by the genetic makeup and other properties of the host. As discussed in the Essay by **Paul Kellam and Robin A. Weiss** (PAGE 695), new host genomic information ("infectogenomics") has the potential to illuminate the biology of pathogenesis, provide clues to the factors that make some individuals more prone to disease, and allow for improved disease prognosis and treatment. In some individuals, microbial infections are associated with the development of a chronic inflammatory disease or cancer. **Michael Karin, Toby Lawrence, and Victor Nizet** (PAGE 823) highlight the molecular overlap between responses to pathogen infections and chronic inflammation and suggest a model whereby an initial response to a microbial infection, involving a breach of an epithelial barrier, can lead to chronic activation of the inflammatory response. Their Review discusses the regulation of inflammatory pathways, and what we've learned of inflammatory disease from various mouse models.

Telling the Good Bugs from the Bad



The bacterium *Citrobacter rodentium* adhering to epithelial cells of the mouse colon. Image courtesy of Julian Guttman, Wayne Vogl, and B. Brett Finlay.

Unlike most of the microbes discussed in this issue, those living in the human gut do not generally cause disease, and may in fact be beneficial to their hosts. The biology and diversity of the gut microbiota is covered in a Review by **Ruth E. Ley, Daniel A. Peterson, and Jeffrey I. Gordon** (PAGE 837). The authors analyze the coevolution of microbial gut communities and their human hosts, speculating on the potential selection pressures that act on gut bacteria, including their effect on host fitness. An Essay by **Stanley Falkow** (PAGE 699) provides another perspective on the apparently peaceful interactions between humans and some microbes. Noting that many disease-causing pathogens, including *Helicobacter pylori* and mycobacteria, can exist asymptomatically in most human hosts, the author suggests that such persistent infections may have health benefits and may provide insights into how our immune system keeps microbes at bay.

The Challenges of Vaccine Development

Three Essays examine some of the challenges to developing effective vaccines against devastating diseases such as tuberculosis (TB), AIDS, and malaria. An Essay by **Douglas Young and Christopher Dye** (PAGE 683) discusses approaches to developing a more effective vaccine against TB. The authors explain some of the problems with the BCG vaccine currently in use and other challenges facing TB vaccine development, including the question of whether to focus on preventing infection or preventing disease progression, given that a significant proportion of people in the developing world are already infected with the mycobacteria. In a second Essay, **Daniel C. Douek, Peter D. Kwong, and Gary J. Nabel** (PAGE 677), examine progress towards making an AIDS/HIV vaccine. HIV poses a unique challenge due to its extreme genetic diversity and its stunning ability to evade the host immune response. Nabel suggests a rational approach to vaccine design and highlights some of the political challenges involved in this endeavor. The third Essay by **Andrew Waters** (PAGE 689) discusses how the biology of the *Plasmodium* parasite complicates malaria vaccine design. In addition to antigenic variation, common to many pathogens, the malaria parasite also goes through several different life-cycle stages in the human host and insect vector, complicating vaccine design even further. The author suggests that the availability of the complete genome sequence of *Plasmodium* may help to select the best antigens for vaccine development.

The Review by **Bali Pulendran and Rafi Ahmed** (PAGE 849) examines vaccine development from the perspective of molecular immunology. They examine the interaction between the innate and the adaptive immune systems and suggest that understanding this interface could help in the design of effective vaccines. They identify several unanswered questions that impinge upon vaccine development and suggest that an analysis of successful vaccines could further help to identify factors that affect the efficiency of the immune response.

A major practical challenge facing the development of any vaccine is the funding for research, clinical trials, and ultimately distribution of the product to those who need it most. In an Analysis article, **Ingfei Chen** (PAGE 661) reports on the efforts of the Bill and Melinda Gates Foundation to support global health projects, from vaccine development to distribution in developing countries. Focusing on the Foundation's Grand Challenges in Global Health initiative, the article examines the Foundation's bold approach, some of the scientific projects it funds, and the problems it has encountered in the process.